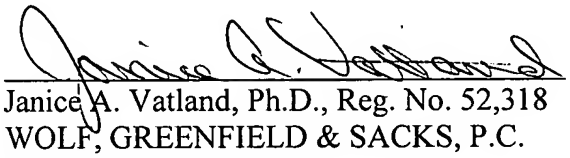
As part of this response, Applicant is also including a copy of the previously-filed Amendment with amended pages of Specification, mailed on May 8, 2006. Applicant believes that this submission is fully responsive to the Notice of Non-Compliant Amendment.

CONCLUSION

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,



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Date: August 22, 2006
x08.25.06

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: **Harry Meade et al.** Art Unit No.: **1632**

Application No.: **10/722,903** Examiner: **Marcia Stephens Noble**

Filed: **November 26, 2003**

For: **MODIFIED ANTIBODIES STABLY PRODUCED IN MILK AND METHODS OF PRODUCING SAME**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA. 22313-1450

COPY

Attorney Docket Number: **GTC-53**

REPLY & AMENDMENT

This Reply and Amendment is being filed in response to the Office Action dated November 9, 2005 in connection with the above identified application. A Response to the November 9, 2005 Office Action was due February 9, 2006 according to the shortened statutory period of three months established by the Examiner in compliance with 35 USC § 133. With the filing of a Petition for a three-month extension of time herewith, this Amendment is being timely filed.

Please amend the application as follows:

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that on May 8, 2006 this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

Dawn C. Greenaway

Amendments to the Specification:

Please replace pages 33 and 34 of the specification with the revised pages attached hereto and being submitted herewith.

Amendments to the Claims:

1. (Currently Amended) A method of producing an antibody in the milk of a non-human transgenic mammal, comprising:

providing a transgenic mammal whose somatic and germ cells comprise a sequence

encoding an exogenous heavy chain variable region or antigen binding fragment thereof, at least one heavy chain constant region, or a fragment thereof, and a hinge region, operably linked to a promoter which directs expression in mammary epithelial cells, wherein said hinge region has been altered from the hinge region normally associated with the heavy chain constant region[[.]];

wherein said alteration is the replacement of at least one serine residue with at least one proline residue.

2. (Original) The method of claim 1, wherein at least 70% of the antibodies present in the milk are in assembled form.

3. (Original) The method of claim 1, wherein said transgenic mammal further comprises a sequence encoding a light chain variable region, or antigen binding fragment thereof, and a light chain constant region or functional fragment thereof, operably linked to a promoter which directs expression in mammary epithelial cells.

4. (Currently Amended) The method of claim 1, further comprising the step of obtaining milk from said transgenic mammal, to thereby provide an antibody composition.

5. (Currently Amended) The method of claim 4, further comprising the step of purifying the exogenous antibody from the milk produced by said transgenic mammal.

6. (Currently Amended) The method of claim 1, wherein said promoter is a promoter selected from the group consisting of: casein promoter, lactalbumin promoter, beta lactoglobulin promoter and whey acid protein promoter.

7. (Currently Amended) The method of claim 1, wherein said transgenic mammal is a mammal selected from the group consisting of: cow, goat, mouse rat, sheep, pig and rabbit.

8. (Currently Amended) The method of claim 1, wherein the antibody is an antibody selected from the group consisting of: IgA, IgD, IgM, IgE or IgG.

9. (Currently Amended) The method of claim 1, wherein the antibody is an IgG antibody.

10. (Currently Amended) The method of claim 1, wherein the antibody is an IgG4 antibody.

11. (Currently Amended) The method of claim 10, wherein all or a portion of the hinge region of said antibody has been altered.

12. (Original) The method of claim 10, wherein all or a portion of the hinge region of the antibody has been replaced, e.g. replaced with a hinge region or portion thereof which differs from the hinge region normally associated with said heavy chain constant region.

13. (Original) The method of claim 10, wherein the amino acid sequence of the hinge region of the antibody differs from the amino acid sequence of the hinge region naturally associated with said heavy chain constant region by at least one amino acid residue.

14. (Currently Amended) The method of claim 1, wherein at least one of the nucleic acid residues of the nucleic acid sequence encoding the hinge region of the antibody ~~differs~~

has been removed or changed from the naturally occurring nucleic acid sequence of the hinge region naturally associated with said heavy chain constant region.

15. (Original) The method of claim 12, wherein the hinge region of the antibody, or portion thereof, has been replaced with the hinge region, or portion thereof, of an antibody other than an IgG4 antibody.

16. (Currently Amended) The method of claim 12, wherein the hinge region, or portion thereof, of the antibody has been replaced with a hinge region, or portion thereof, derived from an antibody selected from a group consisting of: IgG1, IgG2 and IgG3.

17. (Currently Amended) The method of claim 12, wherein the hinge region of the antibody, or a portion thereof, has been replaced with a hinge region, or portion thereof, derived from an antibody selected from a group consisting of: IgA, IgD, IgM and IgE.

18. (Currently Amended) The method of claim 12, wherein one or more amino acids of the hinge region have been replaced with [[an]] a different amino acid ~~corresponding to that position~~ in an antibody other then an IgG4 antibody.

19. (Currently Amended) The method of claim 15, wherein the antibody other than an IgG4 antibody is an antibody selected from the group consisting of: IgA, IgD, IgM and IgE.

20. (Currently Amended) The method of claim 15, wherein the antibody other than an IgG4 antibody is an antibody selected from the group consisting of: IgG1, IgG2 and IgG3.

21. (Original) The method of claim 10, wherein a serine residue of the hinge region has been replaced with a proline residue.

22. (Original) The method of claim 10, wherein a serine residue at amino acid number 241 of the hinge region has been replaced with a proline residue.

23. (Original) The method of claim 10, wherein at least one amino acid in the hinge region other than a cysteine residue is replaced with a cysteine residue.

24. (Currently Amended) The method of claim 10, wherein at least 1 glycosylation site of the antibody is altered.

25. (Original) The method of claim 24, wherein at least one glycosylation site in the heavy chain or light chain is altered.

26. (Original) The method of claim 24, wherein at least one glycosylation site in the hinge region of the heavy chain is modified.

27. (Currently Amended) The method of claim 1, wherein the antibody is humanized.

28. (Currently Amended) The method of claim 1, wherein the antibody is chimeric.

29. (Currently Amended) The method of claim 1, wherein the antibody is a human antibody.

30. (Currently Amended) The method of claim 1, wherein the milk of the transgenic mammal is essentially free from a half molecule form of the exogenous antibody.

31. (Currently Amended) The method of claim 1, wherein the ratio of assembled exogenous antibody to half forms of the antibody present in the milk of a transgenic mammal are at least 2:1, 3:1, 4:1 or 5:1.

32. (Currently Amended) A method of producing a non-human transgenic mammal whose somatic and germ cells comprise a modified antibody coding sequence wherein said modified antibody coding sequence encodes an antibody molecule or portion thereof expressible in milk, comprising a modified hinge region, said method comprising the steps of:

introducing into a mammalian cell line a nucleic acid construct comprising a sequence encoding an exogenous heavy chain variable region or antigen binding fragment thereof, at least one heavy chain constant region or a fragment thereof, and a hinge region, operably linked to a promoter which directs expression in mammary epithelial cells, wherein said hinge region has been altered from the hinge region normally associated with the heavy chain constant region[[.]]; and,

introducing said cell into an embryo or microinjecting a construct into an embryo;

transplanting the embryo into a viable host animal;

screening for the expression of the desired transgene;

wherein the alteration made is to eliminate at least one N-linked glycosylation site on the CH2 region of an antibody's heavy chain constant region.

33. (Currently Amended) The method of claim [[33]] 32, wherein said hinge region has been altered such that at least 70% of the exogenous antibodies present in the milk of the transgenic mammal are in assembled form.

34. (Original) The method of claim 33, wherein said modified antibody coding sequence further comprises a sequence encoding a light chain variable region or antigen binding fragment

thereof and a light chain constant region or functional fragment thereof, operably linked to a promoter which directs expression in mammary epithelial cells.

35. (Currently Amended) The method of claim 33, wherein the promoter is a promoter selected from the group consisting of: casein promoter, lactalbumin promoter, beta lactoglobulin promoter and whey acid protein promoter.

36. (Currently Amended) The method of claim 33, wherein the transgenic mammal is a mammal selected from the group consisting of: cow, goat, mouse rat, sheep, pig and rabbit.

37. (Currently Amended) The method of claim 33, wherein the antibody is an antibody selected from the group consisting of: IgA, IgD, IgM, IgE or IgG.

38. (Currently Amended) The method of claim 33, wherein the antibody is an IgG antibody.

39. (Currently Amended) The method of claim 33, wherein the antibody is an IgG4 antibody.

40. (Currently Amended) The method of claim [40]] 32, wherein all or a portion of the hinge region of the antibody has been altered.

41. (Currently Amended) The method of claim 40, wherein all or a portion of the hinge region of the antibody has been replaced, e.g. replaced with a hinge region or portion thereof which differs from the hinge region normally associated with said heavy chain variable region or said constant region.

42. (Original) The method of claim 40, wherein the amino acid sequence of the hinge region of the antibody differs from the amino acid sequence of the hinge region naturally associated with said heavy chain constant region by at least one amino acid residue.

43. (Original) The method of claim 33, wherein at least one of the nucleic acid residues of the nucleic acid sequence encoding the hinge region of the antibody differs from the nucleic acid sequence of the hinge region naturally associated with said heavy chain constant region.

44. (Currently Amended) The method of claim [[44]] 40, wherein the hinge region of the antibody, or portion thereof, has been replaced with the hinge region, or portion thereof, of an antibody other than an IgG4 antibody.

45. (Currently Amended) The method of claim 42, wherein the hinge region, or portion thereof, of the antibody has been replaced with a hinge region, or portion thereof, derived from an antibody selected from a group consisting of: IgG1, IgG2 and IgG3.

46. (Currently Amended) The method of claim 42, wherein the hinge region of the antibody, or a portion thereof, has been replaced with a hinge region, or portion thereof, derived from an antibody selected from a group consisting of: IgA, IgD, IgM and IgE.

47. (Currently Amended) The method of claim 42, wherein one or more amino acids of the hinge region have been replaced with an amino acid corresponding to that position in an antibody other then an IgG4 antibody.

48. (Currently Amended) The method of claim [[48]] 44, wherein the antibody other than an IgG4 antibody is an antibody selected from the group consisting of: IgA, IgD, IgM and IgE.

49. (Currently Amended) The method of claim 48, wherein the antibody other than an IgG4 antibody is an antibody selected from the group consisting of: IgG1, IgG2 and IgG3.

50. (Original) The method of claim 40, wherein a serine residue of the hinge region has been replaced with a proline residue.

51. (Original) The method of claim 40, wherein a serine residue at amino acid number 241 of the hinge region has been replaced with a proline residue.

52. (Original) The method of claim 40, wherein at least one amino acid in the hinge region other than a cysteine residue is replaced with a cysteine residue.

53. (Currently Amended) The method of claim 40, wherein at least one glycosylation site of the antibody is altered.

54. (Currently Amended) The method of claim 54, wherein at least one glycosylation site in the heavy chain or light chain is altered.

55. (Original) The method of claim 40, wherein at least one glycosylation site in the hinge region of the heavy chain is modified.

56. (Currently Amended) The method of claim 33, wherein the antibody is humanized.

57. (Currently Amended) The method of claim 33, wherein the antibody is a human antibody.

58. (Currently Amended) The method of claim 33, wherein the antibody is chimeric.

59. (Original) The method of claim 33, wherein said hinge region has been altered such that the milk of the transgenic mammal is essentially free from a half molecule form of the exogenous antibody.

60. (Currently Amended) The method of claim 33, wherein the ratio of assembled exogenous antibody to half forms of the antibody present in the milk of a transgenic mammal are at least 2:1, 3:1, 4:1 or 5:1.

61. (Currently Amended) The method of claim 60, wherein the antibody is an antibody selected from the group consisting of: IgA, IgD, IgM, IgE or IgG

62. (Currently Amended) A method of producing a non-human transgenic mammal capable of expressing an assembled exogenous antibody or portion thereof in its milk, the method comprising:

introducing into a mammal a construct comprising a sequence encoding a light chain of exogenous antibody operably linked to a promoter which directs expression in mammary epithelial cells; and

introducing into the mammal a nucleic acid construct comprising a sequence encoding a mutagenized heavy chain of the exogenous antibody or a portion thereof operably linked to a promoter which directs expression in mammary epithelial cells, wherein the heavy chain or portion thereof comprises a hinge region which has been altered such that at least 70% of the exogenous antibodies present in the milk are in assembled form[[.]]; and,

introducing said cell into an embryo or microinjecting a construct into an embryo;

transplanting the embryo into a viable host animal;

screening for the expression of the desired transgene;

wherein at least one amino acid residue present in the hinge region of an Ig molecule has been replaced with a cysteine residue.

63. (Currently Amended) A method of producing a non-human transgenic mammal capable of expressing an assembled exogenous antibody in its milk, the method comprising:

providing a cell from a transgenic mammal whose germ and somatic cells comprise a sequence encoding a light chain of an exogenous antibody operably linked to a promoter which directs expression in mammary epithelial cells; and

introducing into the cell a nucleic acid construct comprising a sequence encoding a mutagenized heavy chain of the exogenous antibody or a portion thereof operably linked to a promoter which directs expression in mammary epithelial cells, wherein the heavy chain, or portion thereof comprises a hinge region which has been altered such that at least 70% of the exogenous antibodies present in the milk are in assembled form[[.]]; and,

introducing said cell into an embryo or microinjecting a construct into an embryo;

transplanting the embryo into a viable host animal;

screening for the expression of the desired transgene;

wherein the entire hinge region of a first Ig molecule has been replaced with the hinge region of a second Ig molecule.

64-89. (Cancelled)

90. (New) The method of claim 1, wherein said at least one serine residue replaced with a proline residue is serine 241 in an IgG4 antibody are in assembled form.

91. (New) The method of claim 32, wherein said alteration made to eliminate at least one N-linked glycosylation site on the CH2 region of an antibody's heavy chain constant region

is an alteration that eliminates an N-linked glycosylation site on the CH2 of an IgG heavy chain by replacing an asparagines residue to a glutamine residue at the consensus site.

92. (New) The method of claim 63 wherein the entire hinge region of a first IgG4 molecule has been replaced with the hinge region of a second IgG molecule

R E M A R K S

The Office Action of November 9, 2005 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is respectfully requested. Applicants thank the Examiner for her thorough and detailed remarks. Claims 1-63 and 90-92 are pending herein. Claims 1, 4-11, 14, 16-20, 24, 27-33, 35-41, 44-49, 53-54, 56-58, 60-63 are amended herein. Claims 64-89 are canceled herein. New claims 90-92 have been added herein.

RESTRICTION REQUIREMENT & FILING OF DIVISIONAL

In reply to the Restriction Requirement in the Office Action mailed November 9, 2005 and in connection with the above identified patent application, Applicant hereby formally elects to continue the prosecution of claims 1-63 drawn to a method of producing an antibody in the milk of a transgenic mammal, classified in class 800, subclass 7, which the Examiner has identified as Group 1. Pursuant to a telephonic interview on October 20, 2005 this election is made without traverse, and Applicants have, in this action, cancelled claims 64-89. However, Applicant retains the right to file a divisional application covering the non-elected invention and the resulting cancelled claims. Given the remarks and amendments made herein it is respectfully proposed that this application is now in condition for allowance. An early and favorable consideration on the merits is earnestly solicited.

INFORMATION DISCLOSURE STATEMENT

Applicants respectfully note at the outset that the IDS documents provided to the Examiner were as complete as Applicant could make them. With regard to the Examiner's concerns – Kabat et al., and EP 467,482 were provided but we herewith attach additional copies. As to FR 2,487,642 it was included in the IDS due to other works that referenced it and because the Applicant's attorney had reviewed an English version of its abstract online. No full English translation is available. Applicant will proceed under the assumption that the IDS issues have been rectified.

COMPLIANCE WITH AMINO ACID AND/OR NUCLEIC ACID SEQUENCES

Per 37 CFR 1.821 through 1.825, the specification has been amended to identify the sequences with the appropriate sequence identifiers. Applicants take this opportunity to point out to the Examiner that the Sequence Listing as originally filed on August 8, 2004 and the Amended Sequence Listing as filed on December 20, 2004 has been further amended herein. Sequence No. 1 was erroneously included in the previous filed Sequence Listings of August 8, 2004 and December 20, 2004. The amended Sequence Listing being filed herewith no longer includes what was identified as Sequence No. 1. There are now 10 total sequences relative to this application, each of which is now identified in the Specification by Sequence ID Nos. and are found in the section of this Reply entitled "Amendments to the Specification."

CLAIM OBJECTIONS

The Examiner objected to claims 33, 40, 44 and 48 under 37 CFR § 1.75(c) as being in improper form for inappropriately reciting dependence from themselves. These errors were clerical in nature and have been rectified through appropriate amendment. Given these amendments the appropriate dependent relationships are restored to claims 33-61. Reconsideration of this objection under MPEP § 608.01 is respectfully requested under paragraph of 35 USC § 112 relative to inability to comply with the written description requirements.

In response, Applicants have made amendments to the claims without prejudice which they believe render moot the Examiner's new grounds of rejection. Applicants, however, respectfully retain that right to re-assert separate claims for physiologically active immunoglobulin fragments in a separate application.

DOUBLE PATENTING

The Examiner has stated that the claims 1-63 stand rejected under the judicially created doctrine of "Double Patenting" relative to Meade et al., patents Nos. 5,827,690 & 5,849,992. Given the current status of the claims in the application this rejection is necessarily in 'provisional' form. Moreover, though not stated by the Examiner, it remains true that for a

commonly owned application a timely filed Terminal Disclaimer filed in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection of this nature. That is, a rejection based on a non-statutory type of double patenting can be avoided by filing a Terminal Disclaimer in the application or proceeding in which the rejection is made. In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); In re Knohl, 386 F.2d 476, 155 USPQ 586 (CCPA 1967); and, In re Griswold, 365 F.2d 834, 150 USPQ 804 (CCPA 1966). It should be noted that the instant application and the patents cited Nos. 5,827,690 & 5,849,992 are commonly owned and exclusively licensed to GTC Biotherapeutics. However, such a filing remains unnecessary as none of the claims in either application have yet been allowed.

Respectfully, at such time that an actual rejection of the pending claims by the Examiner based on the judicially created doctrine of obviousness-type double patenting relative to the claims of United States Patent Applications is made - Applicant will then makes an internal determination as to whether the filing of a terminal disclaimer is appropriate. Such a Disclaimer, should one be filed, would make plain the common ownership of the cited patent application along with the instant patent application. With this filing the claims would be "free" of the cited prior art - without need to traverse the assertion of one over the other. The provisional nature of such a rejection is noted. Abeyance is respectfully requested until such times as the current claims are moved to allowance.

THE REJECTIONS UNDER 35 U.S.C. §101

Claims 1-63 are rejected under 35 U.S.C. §101 as directed to non-statutory subject matter. The claims have been amended to recite "non-human mammal" where needed to traverse this rejection. Reconsideration of the amended claims is respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Pending claims 1-63 are rejected under 35 U.S.C. §112, first paragraph for containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make or use the invention. However, Applicant hereby asserts that despite this broad rejection the claims as amended are in condition for allowance and that the rejection is respectfully traversed.

It first must be pointed out that with respect to biological inventions, as with all other inventions brought before the Patent and Trademark Office, the standard for enablement, as proclaimed in the first paragraph of 35 U.S.C. §112 is the following,

> "[T]he specification shall contain a written description of the invention, and the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

In applying the above standard to the instant claims the issue of adequate enablement then depends on whether one skilled in the art can apply the teachings gained from the working examples present in the specification and known in the prior art regarding the insertion of the desired DNA constructs in the genome of transgenic animals so as to allow the production and separation of desirable proteins from analogous endogenous ones according to the invention. The answer provided by the Federal Circuit on this point is that enablement is not precluded even if some experimentation is required. In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988); In re O'Farrell, 853 F.2d 894, 7 USPQ2 1673 (Fed. Cir. 1988). The only limiting factor is that this experimentation must not be "undue" and that the guidance provided by the Applicant must be only "adequate." In re Vaeck, 947 F.2d 488, at 496 (Fed. Cir. 1991).

NECESSARY EXPERIMENTATION

It must be reiterated that the specification is not required to teach every detail of the invention or to perform the function of a technical production manual/specification. The specification need only explain how to make and use the invention without requiring an inordinate amount of experimentation. The fact that experimentation needed may be complex or even repetitive does not necessarily make it undue if a person skilled in the art typically engages in such experimentation, as in the instant field. In re Borkowski, 422 F.2d 904, 164 USPQ 214 (CCPA 1970). The test of enablement is not even whether experimentation is necessary, but that if experimentation is necessary whether that experimentation is undue. The working examples provided in the specification, and the functional homology of the analogous heterologous antibodies vis-à-vis the antibodies recited in the specification and the prior art provides the

assurance that any needed experimentation will not be "undue" and will amount to little more than routine optimization.

In a broad sense the novelty of the patent lies, as expected, in the novel manipulation and engineering of the transgenic mammal and the method in which production of a desirable, though altered recombinant antibody is reached. The fact that the prior art did not contemplate the type and degree of DNA constructs, or genetic manipulation provided for by Applicants, while the Applicants provide and claim a working example and a written protocol of such is the precise reason why the current application is patentable -- it is novel.

The working protocols disclosed in the specification, provide those in the field the ability to practice the invention, by providing a detailed map leading towards a goal that the Applicant clearly lays out, regardless of the state of the art prior to the application. In conjunction with the extremely high level of skill in the field, it is clear that the specification, as tempered by the relevant case law discussed herein and does provide "adequate" guidance to make and use the invention. Vaeck at 496.

Moreover, and as has been previously and repeatedly stated by the courts:

> "Enablement is a legal issue. The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, hence the specification need not disclose what is well known in the art." In re Myers, 410 F.2d 420, 161 USPQ 668 (CCPA 1969); *and see*, Lindemann Maschinefabrik GMBH v. American Hoist and Derrick Co., 221 U.S.P.Q. 481 (Fed. Cir. 1984).

That is, the issue of adequate enablement depends on whether one skilled in the art could reproduce the claimed invention without "undue experimentation." *See,* Wang Labs, Inc. v. Toshiba Corp., 993 F.2d 858, 26 U.S.P.Q.2d 1601 (Fed Cir. 1993); Utter v Hiraga, 845 F.2d 993, 6 U.S.P.Q.2d 1709 (Fed. Cir. 1988). In Wands Judge Smith decided that the key word in this formula is "undue" not "experimentation" and applied a reasonableness standard as mentioned above, when he stated:

> "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is **merely routine**, or if the specification in question provides a **reasonable amount of guidance with respect to the direction in which the experimentation should proceed**." Wands at 737 (emphasis added).

It should also be remembered that the court in Wands, after the application of all of the Wands factors, held that the Applicants were entitled to claim an assay using any IgM monoclonal antibody having an affinity of at least $10^9 M^{-1}$ for hepatitis B-surface antigen, Wands ***necessarily therefore*** held that the Applicants were entitled to claim ***any*** protein of this class having ***any*** amino structure among a theoretically infinite number of variations in natural or synthetic proteins, as long as they had the same broadly defined and somewhat inexact functional properties as provided in the claims and the limited working examples provided. Wands at 731-37. This along with the Federal Circuit's repeated assertions that in the field of biotechnology the level of skill in the art is necessarily a high one, indicates that the enablement requirements for the instant claims be determined not by the public at large but by scientists already trained in many of the basics of the technology and well-versed in standard protocols. Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 1340 (Fed. Cir. 2000)("Patents, however, are written to enable those skilled in the art to practice the invention, not the public"); Enzo Biochem v. Calgene, Inc., 188 F.3d 1362 (Fed. Cir.1999).

Given the above, therefore, it must be understood that when the Applicants, as in the instant specification:

provide a working example in a transgenic mammalian system;

detail the benefits and methods of optimizing a given nucleic acid sequence for expression in terms of a heterologous protein essentially taking the place of the production of an analogous endogenous protein in a given mammalian transgenic system;

provide a workable means for the insertion of the desired gene construct for the several known elements thereof present in the prior art (see below),

indicate and the type of proteins that could be produced by this method;

incorporate by reference key pieces or prior art that themselves establish the state of the prior art; and

provide guidance to appropriate protocols throughout the specification – including references to old, well-known, and well understood laboratory protocols

then any experimentation that may be necessary, becomes routine. Indeed, the application presents the essential features of the DNA antibody manipulations of transgenic non-human mammals necessary to carry out the invention. Moreover, the Applicants eliminate the

need for any undue experimentation by providing examples in the specification. This level of disclosure is **more than** what is necessary for a specification to provide.

In addition, the amendments made to the claims also appear to ameliorate the Examiner's concerns relative to over-breadth. However, given the above comments reconsideration of the rejection of amended claims 1-63 under 35 U.S.C. § 112, first paragraph, is respectfully requested

New claims 90-92 were added in direct response to the Examiner's statements of enablement and are thought to be enabled for that reason as well as the recitations they contain relative to the underlying amended base claims. Favorable consideration is requested.

THE REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 32, 62 and 63

Independent base claims 32, 62 and 63 are rejected under 35 U.S.C. §112, second paragraph for being incomplete for omitting essential steps in the process of creating a non-human transgenic mammal of the invention. Applicant, respectfully, suggests that the process of creating a transgenic mammal with a definite and identified transgene producing a protein is very long and time-consuming. Applicant notes the Examiner's "missing steps" and has amended the claims accordingly. In the interests of time and brevity Applicant would request if these changes are sufficient to define the development of a non-human transgenic animal? Reconsideration of the rejection of amended claims 32, 62 and 63 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 14, 18, 32 and 62-63

Claims 14, 18, 32 and 62-63 are rejected under 35 U.S.C. §112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. This rejection is respectfully traversed. Each of the rejections enunciated by the Examiner under 35 U.S.C. §112, second paragraph have been addressed through specific amendment to each of the relevant claims.

Claims 30-31 and 59-60

The Examiner has rejected claims 30-31 and 59-60 as being indefinite for the recitation of "half antibody" in the text of the original claims. Respectfully, a "half antibody" is a concept known in the art and consists of a molecular antibody fragment formed from an assembled single light chain and a single heavy chain. This "half antibody" often retains a specific binding site and often contains one or more free sulfhydryl groups in the hinge region. Recitation of this concept is present in the original claims as filed and in the body of the specification. The recitation of this term in the claims can be understood by a worker in the field and is therefore neither vague nor indefinite. Reconsideration of this rejection is respectfully requested. Alternatively, if the Examiner can suggest changes that would be appropriate to the relevant claims given the knowledge of the prior art teachings as to the definition of "half-antibody" Applicant would request such assistance.

THE REJECTIONS UNDER 35 U.S.C. §103(A)

Meade et al., Taylorson et al., Owen et al.,Tan et al., Chuang et al.,

Claims 19, 22 and 25-28 remain rejected under 35 U.S.C. §103(a) as being unpatentable over various combinations of the Meade et al., reference (U.S. Patent No.# 5,827,690)(hereinafter the '690 patent), the Taylorson et al., citation (U.S. Patent No.# 5,985,281)(hereinafter the '281 patent), as well the Owen application US,6204,007, Tan et al., and finally Chuang & Morrison. The rejection of the claims, as amended, is respectfully traversed.

Applicant points first to the amended claims that were so modified to bring further away from the teachings of prior art citations – in particular Meade and Taylorson. Applicant also believes, respectfully, that the Examiner has failed to establishment the required *prima facie* case of obviousness for the amended claims. Therefore, in light of previously presented arguments and without more, the claims are not rendered obvious and should go to issue. In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir.1992).

It is important to point out that there is no requirement in patent law that the a patentable product be produced by non-obvious or novel methods, regardless of whether that product is a DNA construct, or an amino acid sequence but only that the product itself be non-obvious. In re Bell, 26

USPQ2d 1529 (Fed. Cir. 1993); In re Thorpe, 777 F.2d 695, 697, 227 USPQ 964, 966 (Fed. Cir. 1985). As an example, the Federal Circuit upheld this principle in *In re Bell* where the court found that the genes for human insulin like growth factors I and II (IGF) were not rendered obvious by the previously disclosed full amino acid sequences, even narrower than the Examiner's concern here. There has been no similar products to those claimed by the applicant. Bell.

In determining obviousness, the basic issue is whether applied references, alone or in any combination, suggest the claimed invention as a solution to the specific problem solved. When the prior art itself does not suggest or render obvious the claimed solution to that problem, the art involved simply does not satisfy the criteria of 35 U.S.C. § 103 for precluding patentability. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination. Carela v. Starlight Archery, 231 U.S.P.Q. 644 (Fed. Cir. 1986).

The critical inquiry in combining various prior art references is whether there is some reason or motivation to combine present in the prior art as a whole that would motivate a person of ordinary skill in the art to combine those references. Pro-Mold & Tool Co., Inc. v. Great Lake Plastics, Inc., 75 F.3d 1568, at 1573 (Fed. Cir. 1996). When the party challenging patentability relies upon a combination of prior art to so establish, then that party then bears the burden of showing some teaching or suggestion in the references for the combination. Ashland Oil Inc., v. Delta Resins & Refractories, Inc., 776 F.2d 281 (Fed. Cir. 1985). As a Federal Circuit court stated over a decade ago:

> "It is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there must be some teaching, suggestion, or incentive the make the combination made by the inventor." Northern Telecom Inc., v. Datapoint Corp., 121 F.2d 931, 934 (Fed. Cir. 1990). In this sense it is improper to the Applicants ideas as a instruction manual on reconstituting the prior art. R. Harmon, **PATENTS AND THE FEDERAL CIRCUIT** § 4.7 (3d edit. 1994).

No such suggestions were, respectfully, made in the cited prior art and therefore the case for obviousness can be made.

Meade et al.,

As previously stated, the Meade et al, patent provides some insight and teachings in the use of DNA constructs and in the development of transgenic animals for the production of

biopharmaceuticals in milk. However, the teachings of Meade et al., do not by themselves or in combination with any of the other cited art render the instant claims obvious.

The subject matter of the remaining claims is directed to DNA constructs for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal. The construct of the invention includes an appropriate promoter sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence; and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the immunoglobulin protein-coding sequence of interest is inserted into the restriction site.

More to the point for the immediate claims is objective fact that Meade et al., patent fails to provide or teach the following:

I. Meade et al. fails to teach or suggest expressing the light chain and heavy chain of an immunoglobulin separately by using a mammary epithelial cell comprising at least two vectors, one encoding the heavy chain and one encoding the light chain. Meade et al., simply fails to contemplate expressing these chains separately;

II. Meade et al., fails to teach a alterations to the hinge region of the antibody;

III. Meade et al, fails to indicate the utility of changes in glycosylation sites;

IV. Meade et al., fails to teach the unique construction of the restriction site – such that it has a coding sequence inserted into the site- that then allows for a vector which can easily be modified, without the need for cleaving the remaining construct to insert various immunoglobulin chains is an improvement over the prior art. This construction allows for easier expression of a variety of different immunoglobulin coding sequences. Thus, the use a unique restriction site into which the immunoglobulin coding sequence is inserted, adapts to the unique features of expressing immunoglobulins.

As can be seen from the amended claims, each of the above elements provided are present in the specification or explicitly integrated into the pending claims. Given this, and the controlling precedent cited above, the cited art simply fails to render the instant invention obvious. Reconsideration of the rejected claims is respectfully requested.

No Objectively Quantifiable "Suggestion" of Desirability of Combination

When determining the patentability of a claimed invention which combines two known processes or elements, a key question of allowability is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. Lindemann Maschinefabrik GMBH v. American Hoist and Derrick Co., 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984).

That is, the art **must** at least indicate that a combination would be possible and desirable in order to render a future combination of that art obvious to one skilled in the relevant field. Before obviousness may be established, the examiner must show that there is either a suggestion in the art to produce the claimed invention or a compelling motivation based on sound scientific principles. Respectfully, logic compels that the suggestion or motivation be accompanied by a general knowledge of the existence of art recognized techniques for carrying out the proposed invention and that the proposed solution be extant in relevant fields of endeavor such that a reasonable worker in the field would look to them as a source or insight or solutions to existing problems or limitations in the art.. Ex parte Kranz, 19 USPQ2d 1216, at 1217-1218 (1990). *See also,* Ex parte Levengood, 28 USPQ2d 1300, 1301, (Bd. Pat. App. & Int. 1993).

As respectfully provided above there are substantial limitations preventing either Meade or Taylorson, together or alone, from successfully rendering the instant claims obvious. However, they also fail to quantifiably suggest the claimed subject matter to a person of ordinary skill in the art.

It is well accepted that references cannot be combined without some suggestion in the references themselves that such combination may be made. How, then, can the disclosure of a single reference, here Meade et al., be taken to support an allegation of obviousness in the absence not only of any teaching within the reference concerning the individual features alleged to be obvious, but also in the absence of any other reference, here DeBoer et al., showing these

features? The answer is that it cannot. The art presented by the Examiner simply does not accomplish the task.

According to In re Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992), the Examiner may not suggest modifying the references using the present invention as template absent a suggestion of the desirability of the modification and combination in the cited art. No such call for combination is present. Simply piecing together the prior art does not a *prima facie* case of obviousness make. In re Wright 848 F.2d 1216, 6 U.S.P.Q. 2d 1959 (Fed. Cir. 1988). As such, reversal of the instant rejection is respectfully requested.

Other than a fee for the appropriate extension of time no fee is deemed necessary in connection with the filing of this Reply Amendment. However, the Commissioner is authorized to charge any fee which may now or hereafter be due for this application to GTC Biotherapeutics' Deposit Account No. 502092.

Applicants respectfully submit that the pending claims of this application are in condition for allowance, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicant's attorney would advance the prosecution of the case to finality, the Examiner is invited to telephone the undersigned at the number given below.

Early and favorable action is earnestly solicited.

Respectfully Submitted,

Date: 5/8/06

By:

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Amended Pages to Specification

[00126] An antibody heavy chain can be modified using oligonucleotide mutagenesis. Briefly, the desired DNA is altered by hybridizing an oligonucleotide encoding a mutation to a DNA template, where the template is the single-stranded form of a plasmid or bacteriophage containing the unaltered or native DNA sequence of the desired protein. After hybridization, a DNA polymerase is used to synthesize an entire second complementary strand of the template that will thus incorporate the oligonucleotide primer, and will code for the selected alteration in the desired protein DNA. Generally, oligonucleotides of at least 25 nucleotides in length are used. An optimal oligonucleotide will have 12 to 15 nucleotides that are completely complementary to the template on either side of the nucleotide(s) coding for the mutation. This ensures that the oligonucleotide will hybridize properly to the single-stranded DNA template molecule. The oligonucleotides are readily synthesized using techniques known in the art such as that described by Crea et al. (*Proc. Natl. Acad. Sci.* USA, 75: 5765[1978]).

[00127] To effectuate a change from serine to proline at amino acid number 241 of the hinge region, oligonucleotide mutagenesis can be employed using the oligo S241P that will change the serine to proline. The resulting mutant form can be used to generate transgenic mice. The transgenic mice can be milked, and the milk tested for the presence of the antibody and the relative amount of the "half molecule." The sequence of a hinge region of an IgG4 antibody and the oligonucleotideS241P which can be used to mutagenize it are as follows:

IGG4 HINGE REGION

1668 TCTGCA GAG TCC AAA TAT GGT CCC CCA TGC CCA TCA TGC CCA

GGTAAGCCAACCCAGGCCT (SEQ ID NO. 1)

$^{R/S}$ Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro (SEQ ID NO. 2)

S241P OLIGO

GGT CCC CCA TGT CCT CCC TGC CCA GGT AAG CCA (SEQ ID NO. 3)

$^{R/S}$ Gly Pro Pro Cys Pro Pro Cys Pro Gly Lys Pro (SEQ ID NO. 4)

[00128] Further, the entire hinge region of an IgG antibody can be replaced with the hinge region of another antibody. To effectuate this change, an oligonucleotide that codes for the an exon containing the replacement hinge region can be used. The sequence of a hinge

region of an IgG4 antibody and an oligonucleotide which contains an IgG2 replacement hinge region are as follows:

IGG4 HINGE REGION

1662 CTTCTCTCTGCA GAG TCC AAA TAT GGT CCC CCA TGC CCA TCA TGC CCA
GGTCCGCCAACCCAGGC (SEQ ID NO. 5)
R/S Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro(SEQ ID NO. 6)

IGG2 HINGE REGION

1729 CTTCTCTCTGCA GAG CGC AAA TGT TGT GTC GAG TGC CCA CCG TGC CCA
GGTCCGCCAACCCAGGC (SEQ ID NO. 7)
R/S Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro (SEQ ID NO. 8)

[00129] The N-linked glycosylation site on the CH2 of an IgG heavy chain can be eliminated via oligonucleotide mutagenesis using an oligo that causes a change from asparagine to glutamine in the consensus site. The sequence of an oligonucleotide that can effectuate such a change is as follows:

2014 GAG GAG CAG TTC CAG TCT ACT TAC CGA GTG GTC (SEQ ID NO. 9)
R/S Glu Glu Gln Phe Gln Ser Thr Tyr Arg Val Val (SEQ ID NO. 10)

Testing of Mutagenized Versions of Antibodies

[00130] The light chain and mutagenized heavy chain are ligated to the casein promoter and used to generate transgenic mice. Mice are then tested for expression of the antibody as well as the half antibody.

Transgenic Animals

[00131] A founder (F_0) transgenic goat can be made by transfer of fertilized goat eggs that have been microinjected with a construct. The methodologies that follow in this section can be used to generate transgenic goats. The skilled practitioner will appreciate that such procedures can be modified for use with other animals.

Goat Species and Breeds: